



# Association of two specific haplotypes of serotonin transporter gene with fluvoxamine treatment outcome in Iranian patients with obsessive compulsive disorder

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## ABSTRACT

**Introduction:** Converging lines of evidence indicate that serotonin transporter has a role in response to selective serotonin reuptake inhibitors pharmacotherapy in a variety of neuropsychiatric disorders. In the present study, the association of four functional loci of the serotonin transporter gene (*SLC6A4*) with fluvoxamine treatment outcome in Iranian patients with obsessive compulsive disorder (OCD) has been investigated.

**Methods:** A total of 352 Iranian OCD patients were screened for the treatment outcome. Pharmacotherapy was defined as 12 weeks of treatment with fluvoxamine (150-300mg). Finally, 132 patients who had completed their treatment were assigned to three groups (responders, non-responders and refractory) and underwent genotyping for *SLC6A4* variations (STin2, 5-HTTLPR, rs25531 and rs25532) employing PCR-RFLP.

**Results:** Results showed no significant differences between different STin2, 5-HTTLPR/rs25531 and rs25532 single locus genotype frequencies. However, significant associations of two *SLC6A4* haplotypes with treatment response were detected.

**Conclusion:** Detected association of two *SLC6A4* haplotypes with response to fluvoxamine in OCD patients proposed that the research emphasis of OCD pharmacogenetic studies may be placed on haplotype association analyses in candidate genes. This may represent a significant advance over single-locus investigations as a way to understand the influence of genetic factors on drug response in OCD.

## Keywords:

*SLC6A4*

5-HTTLPR

rs25531

rs25532

STin2

## Introduction

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder characterized by recurrent, intrusive and disturbing thoughts accompanied by repetitive behaviors (American Psychiatric Association, 2013). OCD

first-line medications are selective serotonin reuptake inhibitors (SSRI) because of their efficacy and favorable side-effect profiles (Koran et al., 2007). SSRIs usually attenuate the OCD severity in 40–60% of OCD patients by blocking the reuptake of serotonin (5-HT) into the

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pre-synaptic neuron, a process mediated by the serotonin transporter (5-HTT) (Goodman, 1992). Genetic variations are known to have a pivotal role in individual response to SSRI pharmacotherapy since some of the patients don't respond to SSRIs adequately (Weinshilboum, 2003). Converging lines of evidence indicate that 5-HTT which is a protein responsible for the reuptake of serotonin is an important factor in psychiatric disease risk and response to medications (Murphy et al., 2004). The 5-HTT gene, SLC6A4, is located on chromosome 17 (17q11.1–q12) and its most studied variation relates to a polymorphism of the SLC6A4 promoter (5-HTTLPR) (Serretti et al., 2007; Zai et al., 2014). This insertion/deletion polymorphism (5-HTTLPR), reported being 44 base pairs (bp) in length resulted in two common alleles, the long (L) and the short (S) (Lesch and Gutknecht, 2005). The L allele has been demonstrated to generate higher gene expression compared to the S allele allowing more transport sites (Biernacka et al., 2012). The other functional SLC6A4 polymorphism, rs25531, lies just upstream of the 5-HTTLPR in the gene's promoter region. This single nucleotide polymorphism (SNP) is found just in the L allele and acts as a potential modulator of transcription factor binding (Kraft et al., 2005). The rs25531 G allele reduces the SLC6A4 expression to levels nearly equivalent to those of the short allele, whereas the A allele confers higher SLC6A4 expression (Kato et al., 2013). Rs25532 is the other functional SNP in the 5-HTTLPR that is a C to T substitution. Rs25532 T allele leads to a more expressing allele (Wendland et al., 2008). Another genetic region of interest is a variable number tandem repeat polymorphism in the second intron, named STin2. This polymorphism is tri-allelic with 9-, 10-, or 12-repeat alleles. The 12-repeat allele is associated with increased SLC6A4 expression (MacKenzie and Quinn, 1999).

It has been suggested that the SLC6A4 functional variations were associated with inter-individual variability of treatment efficacy of SSRIs (Zhu et al., 2017). Many studies investigated the association of SLC6A4 variations with response to SSRIs in patients with depressive disorders (Kato and Serretti, 2010; Lesch and Gutknecht, 2005; Porcelli et al., 2012; Serretti et al., 2007). There are also pharmacogenetic reports with inconsistent results about the efficacy of SSRIs in OCD patients with different SLC6A4 genotypes (Billett et al., 1997; Denys et al., 2007; Di Bella et al., 2002; Grün-

blatt et al., 2014; McDougle et al., 1998; Miguita et al., 2011; Zhang et al., 2014; Zhang et al., 2004), but there is no report about the association of SLC6A4 variations in Iranian patients with OCD. Since differential 5-HTTLPR effects by ethnicity have been suggested (Bousman et al., 2014; Porcelli et al., 2012; Serretti et al., 2007), we designed the current study to investigate the association of fluvoxamine treatment response in Iranian OCD patients with different SLC6A4 variants.

## Material and methods

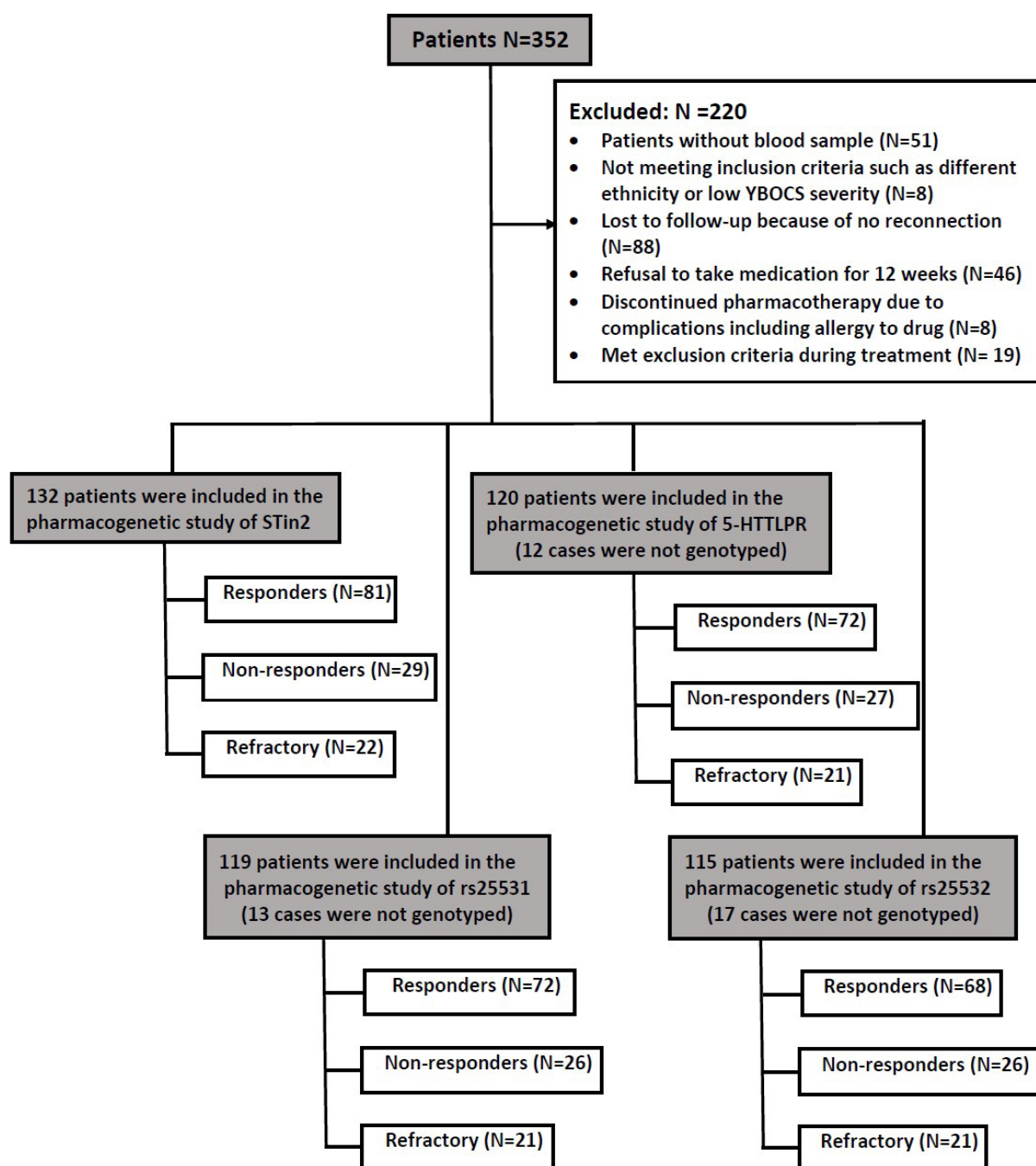
### Subjects

A total of 352 patients with OCD were recruited from the Imam Hossein Hospital in Tehran between 2014 and 2017. All patients were of Iranian descent. The diagnosis of OCD was made according to the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria by an expert psychiatrist. Participants were between the ages of 18 and 65, having OCD symptoms for more than one year and with total Yale-Brown obsessive compulsive scale (Y-BOCS) severity more than 9 (suggested cut-off point for Iranian patients) (Rajezi Esfahani et al., 2012). Y-BOCS is a test to evaluate the severity of obsessive compulsive syndrome. The exclusion criteria were having a history of psychotic disorders or mental retardation, reporting severe neurological pathology, history of substance abuse and diagnosis with other DSM-IV Axis I disorders except for depression, anxiety or tic disorder. OCD patients who were under cognitive behavioral therapy or other pharmacotherapy were also excluded. A drug-free period of at least three weeks was considered as an inclusion criterion for OCD patients. The socio-demographic data and OCD severity were collected through a structured interview using socio-demographic questionnaire and the Persian version of Y-BOCS severity scale, respectively. Pharmacotherapy was defined as 12 weeks treatment with fluvoxamine (150-300mg) as it has been described previously (Hasanpour et al., 2018). Briefly, the escalating fluvoxamine daily dose was initiated from 25mg/day, increased up to 100mg/day for the 3rd week. Fluvoxamine daily dose for the next three weeks was 150mg/day and after the sixth week, patients were visited by the psychiatrist and received maximum tolerated dose of the fluvoxamine for the next 6 weeks. Based on the differences between the first OC severity and the second one after 12 weeks, patients were catego-

rized into two groups: responders, patients that showed more than 35% reduction in Y-BOCS severity score after treatment; non-responders, patients that exhibited less than 35% reduction in Y-BOCS scores (Pallanti and Quercioli, 2006). We've included another group named refractory consisted of patients who showed no change in the severity of their illness or even become worse with all available therapies during their illness period (Pallanti and Quercioli, 2006). This group was different from the non-responders since the latter consisted of patients

who just used fluvoxamine (which was not effective in the reduction of their illness severity) but may respond to other pharmacotherapy strategies. Of the 352 patients with OCD who had participated in this study, 132 patients had completed pharmacotherapy and were included in the pharmacogenetic survey (Figure 1).

All participants gave their written informed consent before enrolling in the study. This study was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.PHNS.



**FIGURE 1.** Flow diagram of the study process.

REC.1397.15).

### Genotyping

Genomic DNA was isolated from peripheral leucocytes by salting out method. Primers were designed to study four SLC6A4 polymorphisms including STin2, 5-HTTLPR, rs25531 and rs25532 (Table 1). PCR am-

plications were performed on an ABi Thermocycler and genotypes for each polymorphism were confirmed by Sanger sequencing of PCR products. A total of 132 cases for STin2, 120 cases for 5-HTTLPR, 119 cases for rs25531 and 115 cases for rs25532 were genotyped (Figure 1).

**TABLE 1:** Primers and PCR-RFLP conditions of SLC6A4 genotyping

SNPs	Primers	Annealing Tem.	Enzyme, Cat No.	Digestion Conditions	Results
STin2	Forward sequence:	63°C	-----	-----	STin2.10: 267 (bp)
	GGGCAATGTCTGGCGCTTCCCCTACATA				STin2.12: 300 (bp)
	Reverse sequence: TTCTGGCCTCTCAAGAGGACCTACAGC				
5-HTTLPR/ rs25531	Forward sequence:	63°C	MspI ER0541	overnight at 37°C	La: 57, 62, 127, 283 (bp)
	GGCGTTGCCGCTCTGAATGC				Lg: 57, 62, 109, 125, 174 (bp)
	Reverse sequence: GAGGGACTGAGCTGGACAACCCAC				Sa: 57, 62, 127, 239
rs25532	Forward sequence: TCCAGCATCCCCCTGCACCT	69°C	BfuI (BcIvI) ER1501	overnight at 37°C	C: 299
	Reverse sequence:				T: 81, 218
	GAGGGACTGAGCTGGACAACCCAC				

### Statistical analysis

All calculations were performed using SPSS 21.00 (SPSS Inc., Chicago, IL). Differences in socio-demographic data and clinical characteristics of three treatment response groups were investigated using chi-square tests or one-way ANOVA followed by Tukey post-hoc. HAPLOTYPE ANALYSIS (Eliades and Eliades, 2009) was used to determine the haplotype frequencies. Serotonin transporter genotype and haplotype frequencies were compared among different treatment response groups employing chi-square statistics. A P-value of  $\leq 0.05$  was used as criteria for statistically significant factors.

## Results

### Subjects

The socio-demographic data and clinical variables for 132 Iranian patients with OCD who completed treatment with fluvoxamine were summarized in Table 2. Comparisons showed that all of the patients who assigned to each treatment response groups had similar socio-demographic data and no differences between them were detected. Responder, non-responder and re-

fractory groups consisted of 62.9%, 65.5% and 63.6% females; 74.1%, 64.3% and 63.6% married and 54.3%, 55.2% and 68.2% unemployed patients, respectively. A total of 87.5%, 68.2% and 84.2% of responder, non-responder and refractory patients reported a family history of psychiatric disorders. Most of the patients in the all treatment response group didn't have academic degrees (school dropout or diploma) (71.6%, 65.6%, and 91% for responder, non-responder and refractory patients, respectively).

The age at assessments of patients in responder, non-responder, and refractory patients (mean $\pm$ SD) were 31.7 $\pm$ 10.1, 34.9 $\pm$ 7.7 and 37.8 $\pm$ 12.1. Patients' age of onset (mean $\pm$ SD) was 23.3 $\pm$ 10.7 in responder group, 22.9 $\pm$ 8.9 in the non-responder group and 22.4 $\pm$ 10.7 in the refractory group. The initial Y-BOCS scores for obsession (mean $\pm$ SD) was 10.9 $\pm$ 5 for responders, 11.6 $\pm$ 4.4 for non-responders and 10.0 $\pm$ 3.8 for refractory patients. The initial compulsion scores for responders, non-responders and refractory patients were 9.3 $\pm$ 5.8, 9.2 $\pm$ 6.2 and 11.2 $\pm$ 3.9, respectively. One-way ANOVA with Tukey post-test showed no significant differences

**TABLE 2:** Sociodemographic characteristics of OCD patients (n=132)

		Responder	Non-responder	Refractory	P-value
Sex, N(%)	Female	51(62.9)	19(65.5)	14(63.6)	0.97
	Male	30(37.1)	10(34.5)	8(36.4)	
Marital status, N(%)	Single	21(25.9)	10(35.7)	8(36.4)	0.15
	Married	60(74.1)	18(64.3)	14(63.6)	
Occupation, N(%)	Unemployed	44(54.3)	16(55.2)	15(68.2)	0.49
	Employed	37(45.7)	13(44.8)	7(31.8)	
Family history, N(%)	Negative	10(12.5)	7(31.8)	3(15.8)	0.46
	Positive	70(87.5)	22(68.2)	19(84.2)	
Education, N(%)	School dropout	19(23.5)	7(24.1)	10(45.5)	0.17
	Diploma	39(48.1)	12(41.4)	10(45.5)	
	Undergraduate	19(23.5)	10(34.5)	1(4.5)	
	Graduate	4(4.9)	0(0.0)	1(4.5)	
Age at assessment	mean	31.7	34.9	37.8	0.09
	SD	10.1	7.7	12.1	
Age of onset	mean	23.3	22.9	22.4	0.93
	SD	10.7	8.9	10.7	
Initial obsession score	mean	10.9	11.6	10.0	0.66
	SD	5.0	4.4	3.8	
Initial compulsion score	mean	9.3	9.2	11.2	0.66
	SD	5.8	6.2	3.9	
Initial total score	mean	19.9	20.1	21.1	0.85
	SD	9.8	9.9	5.3	

N: Number; SD: Standard deviation.



**TABLE 3:** Pharmacogenetic study in three patient groups.

Variation		Responder		Non-responder		Refractory		P-value
		N	%	N	%	N	%	
STin2	10/10	7	8.6	1	3.4	3	13.6	0.52
	10/12	38	46.9	12	41.4	7	31.8	
	12/12	36	44.4	16	55.2	12	54.5	
5-HTTLPR/rs25531	La/La	9	12.5	2	7.7	5	23.8	0.37
	La/Lg	4	5.5	1	3.8	1	4.7	
	La/Sa	30	41.7	12	46.1	4	19.0	
	Lg/Sa	4	5.5	2	7.7	4	19.0	
	Sa/Sa	25	34.7	9	34.6	7	33.3	
rs25532	CC	63	92.6	24	92.3	17	80.9	0.26
	CT	5	7.4	2	7.7	4	19.1	

N: Number.

**TABLE 4:** Haplotype association analysis of *HTR2a* polymorphisms rs6311 and rs6313 with OCD treatment response

Haplotype	STin2	5-HTTLPR	Rs25531	Rs25532	Responders (%)	Non-responders (%)	Refractory (%)	P-value
H1	10	L	a	C	13.2	12.0	17.8	0.24
H2	10	L	a	T	0	0.5	0	0.37
H3	10	L	g	C	1.9	1.9	0.6	0.56
H4	10	L	g	T	0	0	0.6	0.36
H5	10	S	a	C	14.0	12.9	6.5	<b>0.04*</b>
H6	10	S	a	T	0.4	1.4	2.9	0.06
H7	12	L	a	C	20.8	19.7	17.8	0.74
H8	12	L	a	T	0.7	0.5	0	0.36
H9	12	L	g	C	4.1	3.8	10.1	<b>0.00*</b>
H10	12	L	g	T	0	0	0.6	0.36
H11	12	S	a	C	42.0	46.6	37.5	0.17
H12	12	S	a	T	2.6	1.4	5.3	0.08

\*P-value &lt;0.05; The exact P-value for the H9 was 0.008

between initial obsession, compulsion, and total scores of these three groups.

#### Association analyses with *SLC6A4* variations

Both controls and patients were in Hardy-Weinberg equilibrium at each locus investigated. Results of association analysis in three treatment response subgroups showed no significant differences between different STin2, 5-HTTLPR/rs25531 and rs25532 genotypes (Table 3). The frequencies of three genotype groups (L/L, L/S and S/S) were also compared between responders, non-responders as well as refractory and the result showed no significant difference between these three treatment groups (P-value: 0.65). However, significant differences in the frequencies of two *SLC6A4* haplotypes

were detected (H5: 10 S a C and H9: 12 L g C; Table 4). Responders and non-responders showed similar haplotype frequencies for H5 (14.0% and 12.9%) while refractory patients demonstrated less H5 haplotype (6.5%, P-value: 0.040). The frequencies of H9 haplotypes for responder, non-responder and refractory patients were 4.1%, 3.8% and 10.1%, respectively, which showed a significant difference between these three groups (P-value: 0.008).

## Discussion

In the current study, we have focused on a sample of Iranian OCD patients which was treated with a single SSRI, fluvoxamine and investigated the association of four functional *SLC6A4* variations, 5-HTTLPR/

**TABLE 5:** Previous studies investigated the association of SLC6A4 with SRI treatment outcome in OCD patients.

Study	SLC6A4 studied Variations	Drug	Subjects	Ethnicity	Results
(Billett et al., 1997)	5-HTTLPR	10 weeks of treatment at a dosage of 60 mg of fluoxetine per day or 150 mg clomipramine per day, or the maximum dosage that was tolerated (patients who took equivalent doses of fluvoxamine, paroxetine or sertraline were also included in the study).	72 patients	Caucasians	No association
(McDougle et al., 1998)	5-HTTLPR	12 weeks of clomipramine 150–250 mg day <sup>-1</sup> ; fluvoxamine 150–300 mg day <sup>-1</sup> ; fluoxetine 40–80 mg day <sup>-1</sup> ; sertraline 100–200 mg day <sup>-1</sup> ; or paroxetine 40–60 mg day <sup>-1</sup>	34 family trios	Caucasians	higher transmission rate of the L-allele compared with the S-allele in non-responders to SRI treatment (P<0.052), while there was no significant difference in transmission of the L- and S-allele in responders
(Di Bella et al., 2002)	5-HTTLPR	fluvoxamine	92 patients	Caucasian	No association
(Zhang et al., 2004)	5-HTTLPR	SRIs for 8 weeks	113 OCD nuclear families	Chinese	No association
(Denys et al., 2007)	5-HTTLPR	12 weeks dosage titrated upward to 300 mg/day of venlafaxine or 60 mg/day of paroxetine	91 patients	Caucasian	Response in venlafaxine-treated OCD patients is associated with the S/L genotype but 5-HTTLPR is not associated with the paroxetine treatment response
(Miguita et al., 2011)	5-HTTLPR and STin2	clomipramine for 14 weeks	41 OCD patients		No association
(Grünblatt et al., 2014)	5-HTTLPR/rs25531, rs16965628, and rs25532	sertraline (25mg for two weeks)	a 7-year-old boy with rather severe early-onset OCD	Caucasian	Genotype: 5-HTTLPR, LALA; rs25532, CC) rs16965628, GG associated with remission
(Zhang et al., 2014)		fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram and clomipramine	119 OCD patients	Caucasian	Three SNPs across SLC6A4 associated with paroxetine response (p = 0.0006–0.010)

rs25531, rs25532 and STin2 with treatment response. Results showed that none of the single variations associated with response to fluvoxamine but two SLC6A4 haplotypes have significantly different frequencies in various treatment response groups.

Many studies have been published investigating the role of SLC6A4 in response to SSRIs pharmacotherapy in a variety of neuropsychiatric disorders. Studies examining the role of SLC6A4 variations in SSRI treatment response in patients with OCD were presented in Table 5.

Billett et al. (1997) studied the association of 5-HTTLPR with treatment response in 72 OCD patients. They applied 10 weeks of treatment at a dosage of at least 60mg of fluoxetine per day or 150mg clomipramine per day, or the maximum dosage that was tolerated (patients who took equivalent doses of fluvoxamine, paroxetine or sertraline were also included in the study) and found no significant genotypic differences between responders and non-responders groups. McDougle and colleagues (1998) investigated the association of 5-HTTLPR variations with SSRI treatment in 34 European-American trios diagnosed with OCD and detected a very weak association of the L-allele with non-responsiveness in the patients; however, they found no significant difference in transmission of the L- and S-allele in responders. In another study, 92 OCD patients underwent fluvoxamine pharmacotherapy, but no association between 5-HTTLPR genotypes and fluvoxamine response was found (Di Bella et al., 2002). Zhang et al. (2004) studied the association of 5-HTTLPR in a Chinese OCD sample (113 OCD nuclear families) who were treated with SSRIs for eight weeks, and the results showed no association between 5-HTTLPR and SSRI treatment response. Similar results have been reported in a study on 41 OCD patients that were treated with clomipramine for 14 weeks, and no association was detected between 5-HTTLPR and STin2 and treatment response (Migueta et al., 2011). Despite these negative results, there are reports of positive association of serotonin transporter polymorphisms and SSRI treatment response in OCD patients. Denys et al. (2007) detected an association between response in venlafaxine-treated OCD patients with the S/L genotype, although they didn't find the association of 5-HTTLPR with the paroxetine treatment response. There is a case report about a 7-year-old boy with severe early-onset OCD and high functioning serotonin transporter

who respond extraordinarily fast to low-dose sertraline (25mg for two weeks) (Grünblatt et al., 2014). Finally an abstract was presented in the 12th annual pharmacogenetics in psychiatry meeting reported the association of three SNPs across SLC6A4 with paroxetine response ( $P=0.0006-0.010$ ) in 119 OCD patients treated with fluoxetine, fluvoxamine, sertraline, paroxetine and citalopram and clomipramine (Zhang et al., 2014).

Our results are consistent with the investigations reporting no association of SLC6A4 variations especially 5-HTTLPR with response to SSRI treatment in patients with OCD. However, we observed the association of two SLC6A4 haplotypes with response to fluvoxamine. Based on the previous reports, the two significant haplotypes, H5 (10 S A C) and H9 (12 L G C) are functionally the same with the exception of STin2. Functional studies showed that the L variant has been associated to higher expressing function, higher amount of the serotonin transporter, and higher serotonin reuptake activity compared to the S variant (Ehli et al., 2012; Iurescia et al., 2016). However, rs25531 G allele attenuated the gain-of-function of L allele relative to S allele since it creates a binding site for the transcriptional regulator AP2, which exerts a repressive role on the SLC6A4 promoter activity (Hu et al., 2006; Wendland et al., 2008). Although the S and Lg alleles are reported to have the same function, but Murphy et al. (2013) suggested that the functional variations in the SLC6A4 expression can no longer be attributed to the classic S and L, low- and high-expressing alleles, but need to be integrated with the modulating effects of other SLC6A4 polymorphisms, and epigenetic regulatory mechanisms. Findings of the current study supports this hypothesis that the research emphasis may be placed on haplotype association analyses in candidate genes as a way to understand the influence of genetic factors on drug response in OCD.

Similar to other studies we've faced several limitations. Restricted time of pharmacotherapy to 12 weeks is a shortcoming of the current study as the more extended follow-up period may result in more precise evaluation of treatment outcome. The large number of patients who were excluded in different stages of the study because of fluvoxamine side effects or incomplete medication procedure was another limitation of the present study; although statistical analyses of demographic and clinical characteristics showed that excluded patients were



not significantly different compared to the completers. Patients were questioned about adverse life events but their answers were not reliable, so we excluded this item and didn't analyze the association of this factor with SLC6A4 variations. Moreover, fluvoxamine has been administered in a therapeutic dose and was adjusted according to the maximum tolerated dose for each patient, so we can't address dose response relationship with genetic factors. Altogether, replication of the present investigation with independent and larger samples is suggested.

## Conclusion

In conclusion, given the pharmacological evidence favoring a role for serotonin transporter in OCD and SSRI response, further pharmacogenetic investigation of the serotonin transporter in OCD considering haplotype analysis is suggested.

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## Conflict of interest

The authors declare no conflict of interests.

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